## *Remarks*

### *I. The Claims*

Upon entry of the foregoing amendment, claims 1-4, 6-17, 19, 24-37 and 64-80 are pending in the application, with claims 1 and 35 being the independent claims. Claims 1, 24, and 32-35 are sought to be amended. Claims 38-63 are sought to be cancelled. Claims 64-80 are sought to be added. Claims 2-4, and 14-17 are currently withdrawn and are being maintained of record pending rejoinder or the filing of one or more divisional applications. No new matter is added by way of these amendments. It is respectfully requested that the amendments be entered and considered.

Support for the amendment of claims 1 and 35 can be found, *inter alia*, throughout the specification, *e.g.*, page 8, lines 27-32; page 9, lines 1-6; page 19, lines 8-20; page 32, line 20 to page 33, line 10; Figures 5-7; and original claim 34.

Support for new claims 64-70 can be found, *inter alia*, throughout the specification, *e.g.*, page 18, lines 17-28; page 29, lines 12-16; page 30, lines 9-26; Examples 14, 15, 19 and 26; and Table 1. Support for new claim 71 can be found, *inter alia*, throughout the specification, *e.g.*, page 4, lines 8-14 and Example 1. Support for new claims 72-78 can be found, *inter alia*, throughout the specification, *e.g.*, page 5, lines 12-19; page 14, line 14 to page 15, line 2; page 21, lines 8-21; and Examples 3, 4, 15, 20 and 27. Support for new claims 79-80 can be found, *inter alia*, throughout the specification, *e.g.*, Examples 5, 16, 18 and 25.

### *II. Summary of Interview*

Applicants gratefully acknowledge the courtesies extended by Examiner Robert Zeman during a personal interview held March 5, 2008, with Applicants' representative, Doug Golightly.

The claims currently rejected under 35 U.S.C. § 112, second paragraph, were discussed. The Examiner and Applicants' representative discussed amending the claims to clarify "administering" such that the virus or interferon is delivered to the tumor cell. However, no definitive agreement was reached.

The claims rejected under 35 U.S.C. § 112, first paragraph, as requiring a deposit of biological organisms for enablement of the claims were discussed. The Examiner indicated that he was concerned about the availability of the VSV strains, recited in the rejected claims, for the life of the patent. No agreement was reached.

The claims rejected under 35 U.S.C. § 112, first paragraph, as not meeting the enablement requirement were discussed. Applicants' representative discussed that one skilled in the art, based on the teachings of Applicants' specification, could readily make and use the invention commensurate with the scope of the claims. In particular, one skilled in the art could readily utilize the claimed invention, resulting in the reduction of the viability of a hematopoietic tumor cell *in vitro* or *in vivo*. No agreement was reached.

***III. Claim Rejections Under 35 U.S.C. § 112, Second Paragraph***

Claims 1, 5-13, 19 and 24-37 were rejected "under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention". (Office Action, page 3.) Applicants respectfully disagree.

***A. Claim 1***

The Examiner states that claim 1 is "rendered vague and indefinite by the use of the phrase 'administering to the tumor cell a virus'"[1] (Office Action, page 3) and that claim 24 is "rendered vague and indefinite by the use of the phrase 'administering interferon to the tumor cell'" (Office Action, page 4). Applicants respectfully disagree with both of these statements for the reasons already of record, see Applicants' Reply of August 2, 2007.

As mentioned above, during a personal interview the Examiner and Applicants' representative discussed possible claim language to overcome the rejection. Based on these discussions and solely to advance prosecution, and not in acquiescence to the Examiner's rejection, Applicants have amended claim 1 to recite "administering to the tumor cell a virus,

[1] Applicants assume that claims 5-13, 19 and 25-34 are rejected under 35 U.S.C. § 112, second paragraph, solely because they depend (directly or indirectly), from claim 1. Additionally, Applicants assume that claims 35-37 are rejected under 35 U.S.C. § 112, second paragraph, for reciting the phrase "administering a vesicular stomatitis virus". If the Examiner maintains the rejections under 35 U.S.C. § 112, second paragraph, Applicants respectfully request clarification.

such that the virus is delivered to the tumor cell"; amended claim 24 to recite "administering interferon to the tumor cell prior to administering VSV, such that the interferon is delivered to the tumor cell"; and amended claim 35 to recite "administering a vesicular stomatitis virus to the population of cells, such that the virus is delivered to the population of cells". Applicants believe these amendments address the Examiner's concerns and therefore respectfully request the Examiner reconsider and withdraw the rejection of claims 1, 5-13, 19 and 24-37 under 35 U.S.C. § 112, second paragraph.

> As noted in Applicants' previous Reply, the MPEP states,
>
> [e]xaminers are encouraged to suggest claim language to applicants to improve the clarity or precision of the language used, but should not reject claims or insist on their own preferences if other modes of expression selected by applicants satisfy the statutory requirement.

(MPEP § 2173.02 @ 2100-218.) If the Examiner maintains the rejections under 35 U.S.C. § 112, second paragraph, **Applicants would appreciate the Examiner suggesting claim language that he considers acceptable**.

### *IV. Double Patenting Rejection*

Claims 1, 6-13, 24 and 35 are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over (i) claims 1-2 and 7 of copending Application No. 11/671,498 and (ii) claims 1-2 and 6-7 of U.S. Patent No. 7,192,580. (Office Action, pages 4-5.)

Herein, Applicants have amended independent claims 1 and 35 to incorporate elements of previous claim 34. Claim 34 was not rejected for double patenting. Claims 1 and 35 as amended herein relate to, *inter alia*, methods of reducing the viability of a tumor cell, comprising administering a vesicular stomatitis virus, wherein the tumor cell is a hematopoietic tumor cell, wherein the virus is contained in a cell infected with the virus, and the administering comprises administering the virus-infected cell. In contrast, neither (i) claims 1-2 and 7 of copending Application No. 11/671,498 nor (ii) claims 1-2 and 6-7 of U.S. Patent No. 7,192,580 refer to or suggest, *inter alia*, administering a virus-infected cell and therefore, do not render obvious claims 1, 6-13, 24 and 35 as presented herein.

In view of the above, Applicants respectfully request that the Examiner reconsider and withdraw the obviousness-type double patenting rejections of claims 1, 6-13, 24 and 35.

***V. Claims Are Novel and Non-obvious Over Roberts et al.***

The Examiner states, "[c]laims 1, 6-13 and 35 are rejected under 35 U.S.C. 102(a) as being anticipated by or, in the alternative, under 35 U.S.C. 103(a) as obvious over Roberts et al. (WO 99/18799)." (Office Action, page 7.)

An anticipation rejection under 35 U.S.C. § 102 requires a showing that each limitation of a claim is found in a single reference, practice, or device. (*See In re Donohue*, 766 F.2d 531, 534 (Fed. Cir. 1985).)

Applicants have herein amended claims 1 and 35 to relate to, *inter alia*, methods of reducing the viability of a tumor cell, comprising administering a vesicular stomatitis virus, wherein the tumor cell is a hematopoietic tumor cell, wherein the virus is contained in a cell infected with the virus, and the administering comprises administering the virus-infected cell. Roberts *et al.* does not disclose or suggest, *inter alia*, administering a virus infected cell. Therefore, as presented herein, claims 1 and 35 and the claims that depend therefrom, are novel and non-obvious over Roberts *et al.*

In view of the above, Applicants respectfully request that the Examiner reconsider and withdraw the rejection of the claims 1, 6-13 and 35 under 35 U.S.C. § 102(a).

***VI. A Biological Deposit Is Not Required for Enablement***

The Examiner states,

> [c]laims 27-31 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.
>
> It is apparent that the VSV strains MI, M2, M3, M4 and M5 are required in order to practice the invention. The deposit of biological organisms is considered by the Examiner to be necessary for the enablement of the current invention (see 37 CRF [sic] 1.808(a)).

(Office Action, page 8.) Applicants respectfully disagree that a deposit is necessary for the enablement of the present claims.

First, Applicants note that in the outstanding Office Action the Examiner has only made a conclusory statement and has not given reasons why deposits are necessary for the enablement of claims 27-31. Additionally, Applicants remind the Examiner, with regards to an enablement rejection, "[t]he evidence provided by applicant need not be conclusive but merely convincing to one skilled in the art." (MPEP 2164.05 (eighth edition, September 2007); underlining in original.)

A review of the scientific literature indicates that a variety of researchers have had access to the VSV strains of claims 27-31 and new claims 73-77. Because the strains are generally available to researchers in the field, Applicants respectfully submit that deposit under the terms of the Budapest Treaty is not necessary to meet the enablement requirement.

As evidence of the widespread use of these strains, Applicants submit herewith, as part of an Information Disclosure Statement (IDS), copies of the following documents:

- Desforges, *et al.*, Virus Res. (2001) 76(1): 87-102 (Abstract).
- Pasternak, *et al.*, Virology (1988) 166(2): 379-386 (Abstract).
- Marcus *et al.*, J. Gen. Virol. (1980) 47(1): 89-96 (Abstract).
- Ahmed *et al.*, J. Virol. (2003) 77(8): 4646-4657.
- Winship *et al.*, J. Gen. Virol. (1984) 65: 843-847 (Abstract).
- Ferran *et al.*, J. Virol. (1977) 71(1): 371-377.
- Stanners, *et al.*, Cell (1977) 11(2): 273-281 (Abstract).

Desforges *et al.* reports the use of mutant strains T1026 (Ml), TP3 (M3) and G31 (M5). Pasternak *et al.* and Marcus *et al.* report the use of mutant strain T1026 Rl (M2). Ahmed *et al.* reports the use of mutant strains T1026R1 (M2), TP2 and TP3 (M3). Winship *et al.* and Ferran *et al.* reports use of mutant strain T1026R1 (M2). Stanners reports use of mutant strain T1026 (M1). Applicants' specification at page 10, lines 27-29, provides a key to the varying nomenclature in the art for these strains.

As further evidence that the VSV strains recited in claims 27-31 and 73-77 are available, many scientific journals require their authors to agree to make biological materials available to the research community. As evidence, Applicants enclose herewith in Appendix A, the following documents:

- 2005 Instructions to Authors, Journal of Virology (Jan. 2005) 79(1): 1-16
- Guide for Authors, Virology (as downloaded July 13, 2005)

The Instructions to Authors wishing to publish in the Journal of Virology states:

> **[b]y publishing in the journal, the authors agree that any . . . viruses . . . newly described in the article are available from a national collection or will be made available in a timely fashion and at reasonable cost to members of the scientific community for non-commercial purposes**.

(p. 2, left-hand column, last full paragraph; bolding in original) The Guide for Authors wishing to publish in Virology states:

> [p]ublication of a research article in *Virology* is taken to imply that the authors are prepared to distribute freely to academic researchers for their own use any materials (e.g., viruses, cells, DNA clones, antibodies) used in the published experiments.

(Guide for Authors, Editorial Policies.) These policies and similar ones at other journals as well, provide further evidence that mutant VSV strains as recited in claims 27-31 and 73-77 are publicly available to members of the scientific community.

In addition to being available to researchers, these VSV strains are sufficiently described in the specification and in the art so that one skilled in the art can make and use the VSV virus strains recited in claims 27-31 and 73-77. For example, Table 11, Figures 14-23, Example 27 and the Sequence Listing of Applicants' specification provide both nucleic acid and amino acid sequence information for viruses that are the subject matter of claims 27-31 and 73-77.

In summary, Applicants have clearly demonstrated and presented *prima facie* evidence that the viruses recited in claims 27-31 and 73-77 are readily available in the art. In spite of this, during the interview with Applicants' representative on March 5, 2008, the Examiner indicated his concern that the particular viral strains may not continue to be available for the life of the patent. However, the Examiner has not presented any credible reasons or evidence why they

would not continue to be readily available. **Without credible reasons or evidence why they would not continue to be readily available, the burden remains with the Examiner to show that claims 27-31 are not enabled.**

In view of the above, Applicants respectfully request the Examiner reconsider and withdraw the rejection of claims 27-31 under 35 U.S.C. § 112, first paragraph.

### *VII. Claimed Invention is Enabled*

Claims 1, 6-13, 19 and 24-37 were rejected under 35 U.S.C. § 112, first paragraph, because:

> the specification, while being enabling for methods utilizing attenuated VSV for reducing the viability of hematopoietic tumor cells *in vitro* and the use of attenuated VSV to reduce the viability of tumor cell based xenographs in immunodeficient mice, does not reasonably provide enablement for the utilization attenuated VSV for the reduction of viability of all types of hematopoietic tumor cells to reduce the viability of a tumor cell in an immunocompetent animal.

(Office Action, page 9.) Applicants respectfully disagree.

The Examiner seems to base the enablement rejection, at least in part, on the alleged unpredictability of therapeutic results upon practice of the claimed invention. As an example, the Examiner states,

> [p]eople of skill in the art require evidence that a benefit can be derived by the therapeutic application of a given substance; however, a survey of the relevant art does not indicate that substances such as those claimed provide such benefit.

(Office Action, page 19.)[2]

#### *A. Enabled For Reducing The Viability Of A Hematopoietic Tumor Cell*

The Patent and Trademark Office (PTO) bears the initial burden of providing reasons for doubting the objective truth of the statements made by applicants as to the scope of enablement. Only when the PTO meets this burden, does the burden shift to applicants to provide suitable evidence indicating that the specification is enabling in a manner commensurate in scope with

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[2] Applicants respectfully disagree, *inter alia*, that a survey of the relevant art does not indicate that substances such as those claimed provide such benefit, *e.g.*, see the documents listed on page 15 of Applicants previous Reply of August 2, 2007.

the protection sought by the claims. *In re Marzocchi*, 439 F.2d 220, 223, 169 USPQ 367, 369 (CCPA 1971). **The Examiner has not provided reasons for doubting that one skilled in the art could reduce the viability of hematopoietic tumor cells, *in vitro* or *in vivo*, using the claimed methods.**

What is pertinent to meeting the enablement requirement is whether one skilled in the art can make and use the invention commensurate with the scope of the claims. In other words, with regards to the present claims, **can one skilled in the art use the claimed methods to reduce the viability of a hematopoietic tumor cell with administration of a VSV? Applicants have clearly demonstrated this, regardless of whether the administration is *in vitro* or *in vivo*. The Examiner has provided no evidence to the contrary.**

The claims presented herein refer to, *inter alia*, methods of reducing the viability of a tumor cell, comprising administering a vesicular stomatitis virus, wherein the tumor cell is a hematopoietic tumor cell, wherein the virus is contained in a cell infected with the virus, and the administering comprises administering the virus-infected cell. At the time of filing, one skilled in the art, relying on the knowledge in the art and the teachings of Applicants' specification, would have been able to practice the presently claimed invention without undue experimentation, *e.g.*, *in vitro*, *ex vivo* and *in vivo*, even in a human. For example, one skilled in the art, upon review of the specification, would have been able to utilize multiple *in vitro* and *in vivo* methods for administering substances, including virus infected cells, to a tumor cell(s) without undue experimentation. The present specification clearly demonstrates that administering a VSV virus-infected cell to a tumor cell(s), whether *in vitro* or *in vivo* will result in reducing the viability of the tumor cell(s), commensurate with the scope of the present claims. The Examiner's rejection focuses on enabling support for "*in vivo* treatment of hematopoietic tumor cells in humans" (Office Action, page 18; underlining added), not on reducing the viability of a hematopoietic tumor cell(s) comprising administering a VSV virus-infected cell.

***B. Examiner Incorrectly Focuses on Therapeutic Effect and In Vivo Benefit***

The Examiner also states,

the specification does not provide any basis for correlating the *in vitro* results with

> beneficial effects that could reasonably be expected when said viruses are administered *in vivo* to "treat" hematopoietic tumor cells, although *in vivo* use is clearly encompassed by the claims. [sic] Lacking either direct evidence for *in vivo* benefit, or a reasonable basis for correlating the *in vitro* and xenograft data as exemplified in the instant specification with *in vivo* benefit. Hence, the specification cannot be said to teach how to use the claimed viruses as pharmaceuticals without undue experimentation.

(Office Action, page 20, underlining added.) **The Examiner seems to be confusing the differences between therapeutic applications and reducing the viability of a tumor cell.**

The claims presented herein relate to, *inter alia*, methods of reducing the viability of a hematopoietic tumor cell. Even though the subject matter of the present claims encompasses wherein the claimed methods are used to "'treat' hematopoietic tumor cells" (Office Action, page 20), there is no such limitation in any of the present claims. Therefore, the rejection improperly focuses on enabling effective treatment of animals, such as humans.[3] Whether or not a therapeutic reduction of tumor cell viability can be shown or predicted is not pertinent for meeting the enablement requirement with regards to the subject matter of the invention claimed herein, since the claims do not recite any limitations directly related to a therapeutic reduction of tumor cell viability.[3] What is pertinent is whether one skilled in the art can make and use the invention commensurate with the scope of the claims, *i.e.* **to reduce the viability of a hematopoietic tumor cell** with administration of a VSV, commensurate with the claims.

To further support this position, Applicants refer the Examiner to *Ex parte Saito and Zhao* (Appeal No. 2005-1442 before the Board of Patent Appeals and Interferences (BPAI), not binding precedent of the Board; Appendix B) and *Ex parte Boutin* (Appeal No. 2006-1879 before the BPAI, not binding precedent of the Board; Appendix C), which both stand for the proposition that unless the claims explicitly refer to a therapeutic benefit, typically the Examiner should not determine if the claims are enabled for an unclaimed therapeutic benefit. In *Ex parte* Saito and Zhao the Board stated,

> the examiner may be correct that achieving clinically useful gene therapy using the claimed method would require undue experimentation, but the claims are not nonenabled merely for encompassing that difficult-to-achieve outcome.

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[3] For clarity, Applicants believe that, if presented, similar claims to treating hematopoietic tumor cells are enabled by the present application.

(*Ex parte Saito* and Zhao, page 7.) In *Ex parte Boutin* the Board stated,

> [t]his appeal involves claims to a method of transferring nucleic acids into cells, which the examiner has rejected as nonenabled . . . . Because we conclude that enabling the claimed method does not require providing therapeutically effective gene therapy, we reverse.

(*Ex parte Boutin*, page 1.) The *Ex parte Boutin* decision also states,

> when the claims are not directed to a method that achieves a therapeutically useful result, achieving such a result is not required for the claims to be enabled . . . . Thus, while the claims read on gene therapy methods, they do not require producing a clinically effective therapeutic response.

(*Ex parte Boutin*, page 6.)

The claims in both *Ex parte Saito and Zhao* and *Ex parte Boutin* required expression of a gene but did not require a therapeutic result. Both of these decisions stand for the proposition that to satisfy the enablement requirement, all that is required is the expression of the transgene and not a therapeutic benefit. **This is similar to the present application in that the claims require reduction of the viability of a hematopoietic tumor cell, but not a therapeutic benefit. The Examiner has provided no evidence that one skilled in the art would not be able to reduce the viability of a hematopoietic tumor cell, *in vitro* or *in vivo*.** At most, some of the references cited by the Examiner may suggest that some drug candidates with positive results in a xenograft model are not later approved or used as drugs in people. However, **a drug candidate may fail to become an approved drug for various reasons** including (i) the reduction in tumor cell viability may not meet a justifiable or predetermined level, (ii) the general toxicity may be too great, (iii) the therapeutic benefit does not justify the cost and/or (iv) the therapeutic results are not equivalent or better than the standard of care. Therefore, drug candidates can fail to be used as approved treatments **even though they are shown to reduce the viability of tumor cells**, *e.g.*, in a patient. None of these cited references demonstrate or suggest that one skilled in the art would not have been able to reduce the viability of a hematopoietic tumor cell *in vitro* or *in vivo* using the claimed methods.

### *C. Cited Documents Conclude Xenograft Models Are Predictive For Cytotoxic Agents*

**Additionally, several of the documents cited by the Examiner actually conclude that in the case of cytotoxic agents, xenograft models are predictive of clinical outcome.** For example, Peterson and Houghton states:

> from the perspective of drug sensitivity, at least to the conventional cytotoxic agents that comprise most of our current experience, the subcutaneous models appear relatively predictive.

(page 838, first column, underlining added.) Along the same lines, Kelland states

> one may reasonably conclude that, at least for cytotoxic cancer drugs, the human tumour xenograft model, is a good predictor of clinical activity.

(page 83, first column, underlining added.) *Inter alia*, VSV can be thought of as cytotoxic agent for hematopoietic tumor cells. Therefore, the documents cited by the Examiner support a conclusion that the claimed invention is enabled.

***D. Summary***

**No reasons or evidence have been presented that show or suggest that one skilled in the art cannot reduce the viability of a hematopoietic tumor cell *in vitro* or *in vivo*, even in an immunocompetent animal, using the claimed methods. In other words, as long as one skilled in the art at the time of filing, using the teachings of Applicants' specification, could reduce the viability of a hematopoietic tumor cell commensurate with the scope of the claimed methods, the claims are enabled. There has been no evidence presented to the contrary. Therefore, a *prima facie* case for lack of enablement has not been made.**

In view of the above, Applicants respectfully request the Examiner reconsider and withdraw the rejections under 35 U.S.C. § 112, first paragraph.

## *Conclusion*

It is not believed that extensions of time are required beyond those that may otherwise be provided for herein or in accompanying documents. However, if additional extensions of time are necessary to prevent abandonment of this application, The United States Patent and Trademark Office is hereby authorized to charge any fee deficiency required to prevent abandonment of the current application or credit any overpayment to Deposit Account 50-1677.

Applicants believe that a full and complete Reply has been made to the outstanding Office Action and, as such, the present application is in condition for allowance. If the Examiner believes, for any reason, that personal communication will expedite prosecution of this application, the Examiner is invited to telephone the undersigned.

Prompt and favorable consideration of this Amendment and Reply is respectfully requested.

Respectfully submitted,

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Date: April 7, 2008

# Appendix A

JOURNAL OF VIROLOGY, Jan. 2005, p. 1–16
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Vol. 79, No. 1

# JOURNAL OF VIROLOGY

## 2005 INSTRUCTIONS TO AUTHORS*

### SCOPE

The *Journal of Virology* (JVI) is devoted to the timely dissemination of significant knowledge concerning the viruses of plants, fungi, bacteria, protozoa, and animals. Investigators in areas of basic virology are invited to submit reports of original research that uses the approaches of biochemistry, biophysics, cell biology, epidemiology, genetics, genomics, immunology, molecular biology, morphology, proteomics, physiology, and pathogenesis and immunity. The original articles should contain experimental observations that address a hypothesis, lead to new concepts, and indicate new directions in research. Computational analyses of viruses, virus-like sequences, or viral proteins that advance the field are also appropriate. *The journal will not publish papers that simply provide a new restriction map or nucleotide sequence; identify new immunodominant peptides representing T- or B-cell epitopes; or report the isolation or characterization of monoclonal antibodies, a viral variant, or a new strain or type. Such information or reagents must instead be used in further experimentation to test an idea or relate a clear set of novel conclusions that derive from the data.*

JVI specifically encourages publications relating the viruses under study to their host cells or organisms. In recognition of this emphasis, the sections of the journal relating to viral pathogenesis and immunity and to virus-cell interactions have been specifically set aside and identified in the table of contents. The editors wish to promote the publication of research done at the cell biology-virology-organismic biology interface.

JVI also encourages the submission of manuscripts detailing studies in which viruses or viral genetic elements are used as components of vectors for the delivery of therapeutic genes into animals and plants. These original articles should contain experimental observations that lead to new concepts and understanding relevant to gene delivery, regulated expression of therapeutic genes, or viral pathogenesis. To promote publications in this area, the editors have established a section of the journal for articles relating to gene therapy.

JVI encourages manuscripts that include microarrays and similar parallel profiling analyses of viral or cellular gene expression. However, such manuscripts will be published only if they provide novel insight into the biology of the virus or the infected cell, or if they form the basis for additional experiments that provide such insights. It is expected that the primary data from such analyses will be incorporated into the text or figures or will be made available as supplementary material on the ASM website, a publicly accessible laboratory website, or a public repository (such as the National Center for Biotechnology Information).

ASM publishes a number of journals covering various aspects of microbiology. Each journal has a prescribed scope that must be considered in determining where to publish each manuscript. The following guidelines may be of assistance.

(i) JVI will consider papers that describe the use of antiviral agents in elucidating the basic biological processes of viruses and host cells. Papers dealing with other aspects of antiviral agents and chemotherapy will be considered for *Antimicrobial Agents and Chemotherapy.*

(ii) JVI will consider all papers dealing with the biology of bacteriophages. Studies involving the use of bacteriophages as a diagnostic typing system will be considered by the *Journal of Clinical Microbiology.* Those dealing with phages in relation to industrial microbiology will be considered by *Applied and Environmental Microbiology.*

(iii) Manuscripts describing new methods or improvements in media and culture conditions will not be considered by JVI unless the procedures are applied to the study of basic problems in virology or cell biology. Such manuscripts are more appropriate for *Applied and Environmental Microbiology* or the *Journal of Clinical Microbiology.* By the same token, manuscripts dealing with methods for the production of monoclonal antibodies will not be considered unless the methods have been used to address fundamental questions.

(iv) Manuscripts dealing with clinical investigations, excluding those concerned with the activities of antiviral agents, should be submitted to the *Journal of Clinical Microbiology.* Manuscripts dealing with ecology or environmental studies are more appropriate for *Applied and Environmental Microbiology.*

Questions about these guidelines may be directed to the editor in chief of the journal being considered.

If transfer to another ASM journal is recommended by an editor, the corresponding author will be contacted.

**Note that a manuscript rejected by one ASM journal on scientific grounds or on the basis of its general suitability for publication is considered rejected by all other ASM journals.**

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The Council Policy Committee (CPC) of the American Society for Microbiology affirms the long-standing position of the Society that microbiologists will work for the proper and beneficent application of science and will call to the attention of the public or the appropriate authorities misuses of microbiology or of information derived from microbiology. ASM members are obligated to discourage any use of microbiology contrary to the welfare of humankind, including the use of microbes as

* Shading indicates material that has been added or updated.

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Manuscripts submitted to the journal must represent reports of original research, and the original data must be available for review by the editor if necessary.

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By submission of a manuscript to the journal, **the authors guarantee that they have the authority to publish the work and that the manuscript, or one with substantially the same content, was not published previously, is not being considered or published elsewhere, and was not rejected on scientific grounds by another ASM journal.**

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**By publishing in the journal, the authors agree that any plasmids, viruses, and living materials such as microbial strains and cell lines newly described in the article are available from a national collection or will be made available in a timely fashion and at reasonable cost to members of the scientific community for noncommercial purposes.**

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2. **Cox, C. S., B. R. Brown, and J. C. Smith.** J. Gen. Genet., in press.* {*Article title is optional; journal title is mandatory.*}
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3. **Zellnitz, F., and P. M. Foley.** 2 October 1998, posting {*or* revision} date. History of virology. Am. Virol. J. **1**:30–50. [Online.] http://wwwavj.html. {*For online-only journals; page numbers may not be available.*}
4. **Zheng, Z., and J. Zou.** 5 September 2001. The initial step of the glycerolipid pathway: identification of glycerol-3-phosphate/dihydroxyacetone phosphate dual substrate acyltransferases in Saccharomyces cerevisiae. J. Biol. Chem. doi:10.1074/jbc.M104749200. {*For papers published online in manuscript form.*}

NOTE: A URL or DOI is necessary for each online-only reference; a posting or accession date is required for any online reference that is periodically updated or changed.

**(ii) Items cited in the text.** References to unpublished data, articles submitted for publication, meeting abstracts (including those published in journal supplements), personal communications, letters (irrespective of type) and authors' replies to letters, company publications, patent applications and patents pending, computer software, databases, and websites should be made parenthetically in the text as follows.

. . .similar results (R. B. Layton and C. C. Weathers, unpublished data).

. . .system was used (J. L. McInerney, A. F. Holden, and P. N. Brighton, submitted for publication).

. . .in mitochondria (S. De Wit, C. Thioux, and N. Clumeck, Abstr. 34th Intersci. Conf. Antimicrob. Agents Chemother., abstr. 114, 1994).

. . .for other bacteria (A. X. Jones, personal communication).

. . .discussed previously (L. B. Jensen, A. M. Hammerum, R. L. Poulsen, and H. Westh, Letter, Antimicrob. Agents Chemother. **43**:724–725, 1999).

. . . discussed previously (S. L. W. On and P. A. R. Vandamme, Authors' Reply to Letter, J. Clin. Microbiol. **39**:2751–2752, 2001).

. . .the manufacturer (Sigma manual, Sigma Chemical Co., St. Louis, Mo.).

. . .this process (V. R. Smoll, 20 June 1999, Australian Patent Office). {*For non-U.S. patent applications, give the date of publication of the application.*}

. . .information found at the XYZ website (http://cbx_iou.pgr).

. . . the ABC program (version 2.2; Department of Microbiology, State University [http://www.stu.micro]).

**URLs for companies that produce any of the products mentioned in your study or for products being sold may NOT be included in the article. However, company URLs that permit access to scientific data related to the study or to shareware used in the study are permitted.**

## Notes

The Note format is intended for the presentation of brief observations that do not warrant full-length papers. Submit Notes in the same way as full-length papers. *They receive the same review, they are not published more rapidly than full-length papers, and they are not considered preliminary communications.*

Each Note must have an **abstract of no more than 100 words.** Do not use section headings in the body of the

Note; combine methods, results, and discussion in a single section. Paragraph lead-ins are permissible. The text should be kept to a minimum and **should not exceed 1,200 words**; the total number of figures and tables should not exceed four. **Materials and methods should be described in the text, not in figure legends or table footnotes.** Present acknowledgments as in full-length papers, but do not use a heading. The References section is identical to that of full-length papers.

### Minireviews

Minireviews are brief (**limit of 6 printed pages exclusive of references**) summaries of important developments in virology research. They must be based on published articles and may address any subject within the scope of the journal.

Minireviews are solicited by the Minireview editor and are subject to review. Unsolicited reviews will not be considered. Ideas for Minireviews may be sent to the Minireview editor. Manuscripts should be submitted via Rapid Review.

Minireviews do not have abstracts. In the Abstract section of the submission form, put "Not applicable." The body of the Minireview may either have section headings or be set up like a Note (see above).

### Guest Commentaries

Guest Commentaries are invited communications written in response to invitations issued by the editors and concern topics of interest to the broad readership of the journal that are not necessarily covered by Minireviews. They should raise issues of interest to the community of virologists, initiate or focus discussion, or propose position or consensus statements for leadership groups in research. Review of the literature, methods and other how-to papers, and responses targeted at a specific published paper are not appropriate. Guest Commentaries are subject to review.

The length may not exceed 2 printed pages, and the format is like that of a Minireview (see above). Commentaries should be submitted via Rapid Review.

### Letters to the Editor

Two types of Letters to the Editor may be submitted. The first type (Comment Letter) is intended for comments on articles published previously in the journal and must cite published references to support the writer's argument. The second type (New-Data Letter) may report new, concise findings that are not appropriate for publication as full-length papers or Notes.

Letters may be **no more than 500 words long and must be typed double spaced**. Refer to a recently published Letter for correct formatting. Note that authors and affiliations are listed at the foot of the Letter. Provide only the primary affiliation for each author. Authors with the same affiliation must be listed together. The order of author names will be changed as necessary by the Journals staff to avoid repetition of an address.

All Letters to the Editor must be submitted electronically, and the type of Letter (New Data or Comment) must be selected from the drop-down list in the submission form. For Letters commenting on published articles, the cover letter should state the volume and issue in which the article was published, the title of the article, and the last name of the first author. In the Abstract section of the submission form, put "Not applicable." Letters to the Editor do not have abstracts. Both types of Letter must have a title, which must appear on the manuscript and on the submission form. Figures and tables should be kept to a minimum.

If the Letter is related to a published article, it will be sent to the editor who handled the article in question. If the editor believes that publication is warranted, he will solicit a reply from the corresponding author of the article and make a recommendation to the editor in chief. Final approval for publication rests with the editor in chief.

New-Data Letters will be assigned to an editor according to subject matter and will be reviewed by that editor and the editor in chief. Final approval for publication rests with the editor in chief.

**Please note that some indexing/abstracting services do not include Letters to the Editor in their databases.**

### Errata

The Erratum section provides a means of correcting errors that occurred during the writing, typing, editing, or printing (e.g., a misspelling, a dropped word or line, or mislabeling in a figure) of a published article. Send Errata directly to the ASM Journals Department (1752 N St., N.W., Washington, DC 20036-2904, USA), both on disk and in hard copy (**only one hard copy is necessary**). **Please see a recent issue for correct formatting.**

### Authors' Corrections

The Author's Correction section provides a means of correcting errors of omission (e.g., author names or citations) and errors of a scientific nature that do not alter the overall basic results or conclusions of a published article.

For omission of an author's name, the authors of the article and the author whose name was inadvertently omitted must agree, in writing, to publication of the Correction. For other issues involving authorship, including contributions and use or ownership of data and/or materials, all disputing parties must agree, in writing, to publication of the Correction. Copies of the agreement letters must accompany the Correction and be sent directly to the Journals Department. Send the Correction both on disk and in hard copy (**only one hard copy is necessary**). **Please see a recent issue for correct formatting.**

Corrections of a scientific nature (e.g., an incorrect unit of measurement or order of magnitude used throughout; contamination of one of numerous cultures; or misidentification of a mutant strain, causing erroneous data for only

a portion [noncritical] of the study) must be sent, both on disk and in hard copy, directly to the editor who handled the article and must be accompanied by *signed letters of agreement* from all of the authors of the article. If the editor believes that publication is warranted, he will send the Correction to the Journals Department for publication. Note that the addition of new data is not permitted.

### Retractions

Retractions are reserved for major errors or breaches of ethics that, for example, may call into question the source of the data or the validity of the results and conclusions of an article. Send a Retraction and an accompanying explanatory letter *signed by all of the authors* directly to the editor in chief of the journal. The editor who handled the paper and the chairman of the ASM Publications Board will be consulted. If all parties agree to the publication and content of the Retraction, it will be sent to the Journals Department for publication.

## ILLUSTRATIONS AND TABLES

**Digital files that are acceptable for production (see below) must be provided for all illustrations on return of the modified manuscript. (On initial submission, the entire paper may be submitted in PDF format.)**

**We strongly recommend that before returning their modified manuscripts, authors check the acceptability of their digital images for production by running their files through Rapid Inspector,** a tool provided at the following URL: http://rapidinspector.cadmus.com/rnw/. Rapid Inspector is an easy-to-use Web-based application that takes only minutes to identify problems that may cause the file to fail at any point during the production process.

Illustrations may be continuous-tone photographs, line drawings, or composites. Color graphics may be submitted, but the cost of printing in color must be borne by the author. Suggestions about how to reduce costs and ensure accurate color reproduction are given below.

In general, digital files are not used for tables at the production stage; however, restrictions on file formats still apply (see the section on Tables below).

Since the contents of computer-generated images can be manipulated for better clarity, the Publications Board at its May 1992 meeting decreed that a description of the software/hardware used should be put in the figure legend(s).

### Illustrations

**File types and formats.** As mentioned above, illustrations may be supplied as PDF files for reviewing purposes only on initial submission; in fact, we recommend this option to minimize file upload time. At the modification stage, production quality digital files must be submitted: TIFF or EPS files from supported applications or PowerPoint files (black and white only). Except

**Macintosh**

| Application | File type | |
|---|---|---|
| | Black and white | Color (CMYK)[a] |
| Adobe Illustrator 6.0, 7.0, 8.0, 9.0, and 10.0 | EPS | EPS |
| Adobe InDesign 1.0 | EPS | EPS |
| Adobe PageMaker 6.5 | EPS | EPS |
| Adobe Photoshop | | |
| 4.0 | TIFF | TIFF |
| 5.0 | TIFF | TIFF |
| 5.0 LE | TIFF | N/A[b] |
| 5.5 | TIFF | TIFF |
| 6.0 | TIFF | TIFF |
| ChemDraw Pro 5.0 | EPS/TIFF | EPS/TIFF |
| Corel Photo-Paint 8.0 | TIFF | EPS |
| CorelDRAW 6.0 and 8.0 | EPS/TIFF | EPS |
| Deneba Canvas 5.0, 6.0, 7.0, and 8.0 | EPS/TIFF | EPS |
| Macromedia FreeHand 7.0, 8.0, and 9.0 | EPS | EPS |
| PowerPoint '98 and 2001 | PPT[c] | N/A[b] |
| Prism 3 by GraphPad | TIFF | N/A[b] |
| QuarkXpress | EPS | EPS |
| Synergy Kaleidagraph 3.08 and 3.51 | EPS | N/A[b] |

[a] Color graphics must be saved and printed in the CMYK mode, *not* RGB.
[b] ASM accepts only black-and-white, not color, graphics created with Kaleidagraph, Adobe Photoshop 5.0 LE, Prism 3 by GraphPad, and PowerPoint.
[c] For instructions on saving PowerPoint files, refer to the Cadmus digital art website at http://cjs.cadmus.com/da.

**Windows**

| Application | File type | |
|---|---|---|
| | Black and white | Color (CMYK)[a] |
| Adobe Illustrator 7.0, 8.0, and 9.0 | EPS | EPS |
| Adobe InDesign 1.0 | EPS | EPS |
| Adobe PageMaker 6.5 | EPS | EPS |
| Adobe Photoshop | | |
| 4.0 | TIFF | TIFF |
| 5.0 | TIFF | TIFF |
| 5.0 LE | TIFF | N/A[b] |
| 5.5 | TIFF | TIFF |
| 6.0 | TIFF | TIFF |
| ChemDraw Pro 5.0 | EPS/TIFF | EPS/TIFF |
| Corel Photo-Paint 8.0 and 9.0 | TIFF | EPS |
| CorelDRAW 7.0, 8.0, and 9.0 | EPS/TIFF | EPS |
| Deneba Canvas 6.0 and 7.0 | EPS/TIFF | EPS |
| Macromedia FreeHand 7.0, 8.0, and 9.0 | EPS | EPS |
| PowerPoint '97, 2000, and XP | PPT[c] | N/A[b] |
| Prism 3 by GraphPad | TIFF | N/A[b] |
| QuarkXpress | EPS | EPS |
| SigmaPlot 8.01 | EPS | EPS |

[a] Color graphics must be saved and printed in the CMYK mode, *not* RGB.
[b] ASM accepts only black-and-white, not color, graphics created with Adobe Photoshop 5.0 LE, Prism 3 by GraphPad, and PowerPoint.
[c] For instructions on saving PowerPoint files, refer to the Cadmus digital art website at http://cjs.cadmus.com/da.

for figures produced in PowerPoint, all graphics submitted with modified manuscripts must be bitmap, grayscale, or CMYK (*not* RGB). Acceptable file types and formats for production are given in the tables below. More-detailed instructions for preparing illustrations are available on the World Wide Web at http://cjs.cadmus.com/da. Please review this information before preparing your files. If you require additional information, please send an e-mail inquiry to digitalart@cadmus.com.

**Minimum resolution.** It is extremely important that a high enough resolution is used. Note, however, that the higher the resolution, the larger the file and the longer the upload time. Publication quality will *not* be improved by using a resolution higher than the minimum. Minimum resolutions are as follows:

300 dpi for grayscale and color
600 dpi for lettering
1,200 dpi for line art

Resolution requirements do not apply to graphics created in PowerPoint.

**Size.** All graphics **MUST be submitted at their intended publication size**; that is, the image uploaded should be 100% of its print dimensions so that no reduction or enlargement is necessary. Include only the significant portion of an illustration. White space must be cropped from the image, and excess space between panel labels and the image must be eliminated.

Maximum width for a 1-column figure: 3⅜ inches (ca. 8.4 cm)
Maximum width for a 2-column figure: 6⅞ inches (ca. 17.4 cm)
Minimum width for a 2-column figure: 4¼ inches (10.8 cm)
Maximum height: 9⅛ inches (25.3 cm)

**Contrast.** Illustrations must contain sufficient contrast to withstand the inevitable loss of contrast and detail inherent in the printing process. See also the section on color illustrations below.

**Labeling and assembly.** All final lettering, labeling, tooling, etc., MUST be incorporated into the figures. It cannot be added at a later date. If a figure number is included, it must appear well outside the boundaries of the image itself. (Numbering may need to be changed at the copyediting stage.) Each figure must be uploaded as a separate file, and any multipanel figures must be assembled into one file; i.e., rather than uploading a separate file for each panel in a figure, assemble all panels in one piece and supply them as one file.

**Fonts.** To avoid font problems, set all type in one of the following Type 1 PostScript fonts: Helvetica, Times Roman, European PI, Mathematical PI, or Symbol. All fonts other than these five must be converted to paths (or outlines) in the application with which they were created. For font use in PowerPoint images, refer to the Cadmus digital art website, http://cjs.cadmus.com/da.

**Compression.** Images created with Macintosh applications may be compressed with Stuffit. Images created with Windows applications may be compressed with WINZIP.

**Color illustrations.** Because the process of placing ink on paper by using printing presses is different from that used to produce a photo print or a laser print and the color rendition on images viewed on a monitor depends to some extent on monitor resolution, some differences in color and contrast between the image you submit and the image printed in the journal or published online will be evident. (Figures showing red or green fluorescence and those with a significant range of colors may be difficult or impossible to reproduce exactly.) Color illustrations must be saved as either TIFF or EPS files, according to the application used (see charts above). The mode of the TIFF or EPS file must be CMYK, *not* RGB. Graphics in the RGB color space are intended for display on a monitor only and will not separate correctly for printing.

*The cost of printing in color must be borne by the author.* The current color costs may be accessed from the submission form in Rapid Review. Adherence to the following guidelines, in addition to the general ones above, will help to minimize costs and to ensure color reproduction that is as accurate as possible.

Include only the significant portions of illustrations so that the number of printed pages containing color figures is minimized. The individual panels of a single figure must be assembled in a single file, including any necessary labels. Optimal color reproduction will be obtained if the composites comprise panels containing similar colors of similar lightness or darkness. If necessary, make unlike panels into separate figures/files; this will increase the cost, but the color rendition will be more accurate since the two panels will be "scanned" separately.

## Drawings

Submit graphs, charts, complicated chemical or mathematical formulas, diagrams, and other drawings as finished products not requiring additional artwork or typesetting. No part of the graph or drawing may be handwritten. *All* elements, including letters, numbers, and symbols, *must* be easily readable, and both axes of a graph must be labeled. Keep in mind that the journal is published both in print and online and that the same electronic files submitted by the authors are used to produce both.

When creating line art, please use the following guidelines:

1. **All art MUST be submitted at its intended publication size.** For acceptable dimensions, see the Size section above.

2. **Avoid using screens (i.e., shading)** in line art. It can be difficult and time-consuming to reproduce these images without moiré patterns. Various pattern backgrounds are preferable to screens as long as the patterns are not imported from another application. If you must use images containing screens,

   - Generate the image at line screens of 85 lines per inch or lower.
   - When applying multiple shades of gray, differentiate the gray levels by at least 20%.
   - Never use levels of gray below 20% or above 70% as they will fade out or become totally black upon scanning and reduction.

3. Use thick, solid lines that are no finer than 1 point in thickness.

4. No type should be smaller than 9 point at the final publication size.

5. Avoid layering type directly over shaded or textured areas.

6. Avoid the use of reversed type (white lettering on a black background).

7. Avoid heavy letters, which tend to close up, and unusual symbols, which the printer may not be able to reproduce in the legend.

8. If colors are used, avoid using similar shades of the same color and avoid very light colors.

In figure ordinate and abscissa scales (as well as table column headings), **avoid the ambiguous use of numbers with exponents.** Usually, it is preferable to use the Système International d'Unités (SI) symbols ($\mu$ for $10^{-6}$, m for $10^{-3}$, k for $10^{3}$, M for $10^{6}$, etc.). A complete listing of SI symbols can be found in the International Union of Pure and Applied Chemistry (IUPAC) "Manual of Symbols and Terminology for Physicochemical Quantities and Units" (Pure Appl. Chem. **21**:3–44, 1970). Thus, a representation of 20,000 cpm on a figure ordinate is to be made by the number 20 accompanied by the label kcpm.

When powers of 10 must be used, the journal requires that the exponent power be associated with the number shown. In representing 20,000 cells per ml, the numeral on the ordinate would be "2" and the label would be "$10^4$ cells per ml" (not "cells per ml $\times$ $10^{-4}$"). Likewise, an enzyme activity of 0.06 U/ml would be shown as 6 accompanied by the label $10^{-2}$ U/ml. The preferred designation would be 60 mU/ml (milliunits per milliliter).

### Presentation of Nucleic Acid Sequences

Nucleic acid sequences of limited length which are the primary subject of a study may be presented freestyle in the most effective format. Longer nucleic acid sequences must be presented as figures in the following format to conserve space. Print the sequence in lines of approximately 100 to 120 nucleotides in a nonproportional (monospace) font that is easily legible when published with a line length of 6 inches (ca. 15.2 cm). If possible, lines of nucleic acid sequence should be further subdivided into blocks of 10 or 20 nucleotides by spaces within the sequence or by marks above it. Uppercase and lowercase letters may be used to designate the exon-intron structure, transcribed regions, etc., if the lowercase letters remain legible at a 6-inch (ca. 15.2-cm) line length. Number the sequence line by line; place numerals, representing the first base of each line, to the left of the lines. **Minimize spacing between lines of sequence, leaving room only for annotation of the sequence.** Annotation may include boldface, underlining, brackets, boxes, etc. Encoded amino acid sequences may be presented, if necessary, immediately above or below the first nucleotide of each codon, by using the single-letter amino acid symbols. Comparisons of multiple nucleic acid sequences should conform as nearly as possible to the same format.

### Figure Legends

Legends should provide enough information so that the figure is understandable without frequent reference to the text. However, detailed experimental methods must be described in the Materials and Methods section, not in a figure legend. A method that is unique to one of several experiments may be reported in a legend only if the discussion is very brief (one or two sentences). Define all symbols used in the figure and define all abbreviations that are not used in the text.

### Tables

Tables that contain artwork, chemical structures, or shading must be submitted as illustrations in an acceptable format at the modification stage. Regular tables must be submitted either as Word, WordPerfect, or Acrobat PDF files. Note that a straight Excel file is *not* an acceptable format. Excel files must either be embedded in a Word or WordPerfect document or be converted to PDF *before* being uploaded. Although PDF files and word processing files with embedding are *not* generally acceptable for production purposes, they *are* acceptable for tables. Unlike the other parts of a manuscript, tables are not produced from the author's source files. They must be rekeyed by the printer before going into a page composition program. **If your modified manuscript contains PDF tables, select "for reviewing purposes only" at the beginning of the file upload process.**

Tables should be formatted as follows. Arrange the data so that **columns of like material read down, not across.** The headings should be sufficiently clear so that the meaning of the data is understandable without reference to the text. See the Abbreviations section (p. 15) of these Instructions for those that should be used in tables. Explanatory footnotes are acceptable, but more extensive table "legends" are not. Footnotes should not include detailed descriptions of the experiment. Tables

must include enough information to warrant table format; those with fewer than six pieces of data will be incorporated into the text by the copy editor. Table 1 is an example of a well-constructed table.

TABLE 1. Distribution of protein and ATPase in fractions of dialyzed membranes[a]

| Membrane | Fraction | ATPase | |
|---|---|---|---|
| | | U/mg of protein | Total U |
| Control | Depleted membrane | 0.036 | 2.3 |
| | Concentrated supernatant | 0.134 | 4.82 |
| E1 treated | Depleted membrane | 0.034 | 1.98 |
| | Concentrated supernatant | 0.11 | 4.6 |

[a] Specific activities of ATPase of nondepleted membranes from control and treated bacteria were 0.21 and 0.20, respectively.

### Cover Photographs and Drawings

JVI publishes photographs and drawings on the front cover. Invitations are issued to authors whose manuscripts are returned for modification or whose manuscripts have been accepted for publication in JVI; material should be related to the work presented in the manuscript. Unsolicited material will also be considered, however. No material submitted for consideration will be returned to the author. Copyright for the chosen material must be transferred to ASM. A short description of the cover material will be included at the end of the table of contents or the author index of the issue. Technical specifications are available from the cover editor, Daniel DiMaio (e-mail: daniel.dimaio@yale.edu).

## NOMENCLATURE

### Chemical and Biochemical Nomenclature

The recognized authority for the names of chemical compounds is *Chemical Abstracts* (Chemical Abstracts Service, Ohio State University, Columbus) and its indexes. *The Merck Index*, 13th ed. (Merck & Co., Inc., Whitehouse Station, N.J., 2001), is also an excellent source. For biochemical terminology, including abbreviations and symbols, consult *Biochemical Nomenclature and Related Documents* (1978; reprinted for The Biochemical Society, London, England) and the instructions to authors of the *Journal of Biological Chemistry* and the *Archives of Biochemistry and Biophysics* (first issues of each year).

Do not express molecular weight in daltons; molecular weight is a unitless ratio. Molecular mass is expressed in daltons.

For enzymes, use the recommended (trivial) name assigned by the Nomenclature Committee of the International Union of Biochemistry (IUB) as described in *Enzyme Nomenclature* (Academic Press, Inc., New York, N.Y., 1992). If a nonrecommended name is used, place the proper (trivial) name in parentheses at first use in the abstract and text. Use the EC number when one has been assigned, and express enzyme activity either in katals (preferred) or in the older system of micromoles per minute.

For nomenclature of restriction enzymes, DNA methyltransferases, homing endonucleases, and their genes, refer to the article by Roberts et al. (Nucleic Acids Res. 31:1805–1812, 2003).

### Nomenclature of Mice

For mouse strain and genetic nomenclature, ASM encourages authors to refer to the guidelines set forth by the International Committee on Standardized Genetic Nomenclature for Mice, available on the Mouse Genome Database home page at http://www.informatics.jax.org and in *Genetic Variants and Strains of the Laboratory Mouse*, 3rd ed. (M. F. Lyon et al., ed., Oxford University Press, Oxford, England, 1996).

### Nomenclature of Viruses

Names used for viruses should be those approved by the International Committee on Taxonomy of Viruses (ICTV) and published in *Virus Taxonomy: Classification and Nomenclature of Viruses, Seventh Report of the International Committee on Taxonomy of Viruses* (M. H. V. van Regenmortel et al., ed., Academic Press, San Diego, Calif., 2000). In addition, the recommendations of the ICTV regarding the use of species names should generally be followed: when the entire species is discussed as a taxonomic entity, the species name, like other taxa, is italic and has the first letter and any proper nouns capitalized (e.g., *Tobacco mosaic virus*, *Murray Valley encephalitis virus*). When the behavior or manipulation of individual viruses is discussed, the vernacular (e.g., tobacco mosaic virus, Murray Valley encephalitis virus) should be used. If desired, synonyms may be added parenthetically when the name is first mentioned. Approved generic (or group) and family names may also be used.

### Nomenclature of Bacteria

Binary names, consisting of a generic name and a specific epithet (e.g., *Escherichia coli*), should be used for all bacteria. Names of categories at or above the genus level may be used alone, but specific and subspecific epithets may not. A specific epithet must be preceded by a generic name, written out in full the first time it is used in a paper. Thereafter, the generic name should be abbreviated to the initial capital letter (e.g., *E. coli*), provided there can be no confusion with other genera used in the paper. Names of all taxa (kingdoms, phyla, classes, orders, families, genera, species, and subspecies) are printed in italics; strain designations and numbers are not.

### Genetic Nomenclature

To facilitate accurate communication, **it is important that standard genetic nomenclature be used whenever possible and that deviations or proposals for new naming systems be endorsed by an appropriate authoritative body**. Review and/or publication of submitted manuscripts that contain new or nonstandard nomenclature may be delayed by the editor or the Journals Department so that they may be reviewed by the Genetics and Genomics Committee of the ASM Publications Board.

Before submission of manuscripts, authors may direct questions on genetic nomenclature to the committee's chairman: Maria Costanzo (e-mail: maria@genome.stanford.edu). Such a consultation should be mentioned in the manuscript submission letter.

When appropriate for viral genetic systems, use the recommendations of Demerec et al. (Genetics **54**:61–76, 1966) as a guide.

(i) Phenotype designations must be employed when mutant loci have not been identified or mapped. They can also be used to identify the protein product of a gene, e.g., the OmpA protein. Phenotype designations generally consist of three-letter symbols; these are *not* italicized and the first letter of the symbol is capitalized. It is preferable to use Roman or Arabic numerals (instead of letters) to identify a series of related phenotypes. Thus, a series of bacteriocin-tolerant mutants might be designated TolI, TolII, TolIII, etc., or a series of nucleic acid polymerase mutants might be designated Pol1, Pol2, Pol3, etc. Wild-type characteristics can be designated $Tol^+$ or $Pol^+$, and, when necessary for clarity, negative superscripts ($Tol^-$ $Pol^-$) can be used to designate mutant characteristics. Lowercase superscript letters may be used to further delineate phenotypes (e.g., $Str^r$ for streptomycin resistance). Phenotype designations should be defined.

(ii) Genotype designations are also indicated by three-letter locus symbols. These are lowercase italic (e.g., *pol src*). If several loci govern related functions, these are distinguished by italicized capital letters following the locus symbol.

(iii) Wild-type alleles are indicated with a superscript plus ($ara^+$ $his^+$). A superscript minus is not used to indicate a mutant locus; thus, one refers to an *ara* mutant rather than an $ara^-$ strain.

(iv) The rules for genetic nomenclature of viruses (phages) differ from those of bacteria. As a general rule, the entire description of a virus is italicized, including the designations *am* or *sus* (amber suppressible) and *ts* (temperature sensitive). Superscripts are employed to indicate hybrid genomes. Genetic symbols may be one, two, or three letters. For example, a mutant strain of λ might be designated λ *cI*857 *int*2 *red*114 *susA*11; this strain carries mutations in genes *cI*, *int*, and *red* and a suppressible (*sus*) mutation in gene *A*. A strain designated $\lambda$ $imm^{21}$ $att^{434}$ would represent a hybrid of phage λ which carries the immunity (*imm*) region of phage 21 and the attachment (*att*) region of phage 434. Host DNA insertions into viruses should be delineated by square brackets, and the genetic symbols and designations for such inserted DNA should conform to those employed for the host genome. Genetic symbols for phage λ can be found in reports by Echols and Murialdo (Microbiol. Rev. **42**:577–591, 1978) and Szybalski and Szybalski (Gene **7**:217–270, 1979).

**"Mutant" versus "mutation."** Authors are reminded of the distinction between a *mutation* (an alteration of the primary sequence of the genetic material) and a *mutant* (a strain carrying one or more mutations). One may speak about the mapping of a mutation, but one cannot map a mutant. Likewise, a mutant has no genetic locus, only a phenotype.

**"Homology" versus "similarity."** For use of terms that describe relationships between genes, consult the articles by Theissen (Nature **415**:741, 2002) and Fitch (Trends Genet. **16**:227–231, 2000).

"Homology" implies a relationship between genes that share a common evolutionary origin; partial homology is not recognized. When sequence comparisons are discussed, it is more appropriate to use the term "percent sequence similarity" or "percent sequence identity," as appropriate.

## ABBREVIATIONS AND CONVENTIONS

### Verb Tense

ASM strongly recommends that for clarity you use the **past** tense to narrate particular events in the past, including the procedures, observations, and data of the study that you are reporting. Use the present tense for your own general conclusions, the conclusions of previous researchers, and generally accepted facts. Thus, most of the abstract, Materials and Methods, and Results will be in the past tense, and most of the introduction and some of the Discussion will be in the present tense.

Be aware that it may be necessary to vary the tense in a single sentence. For example, it is correct to say "White (30) demonstrat*ed* that XYZ cells *grow* at pH 6.8," "Figure 2 shows that ABC cells fail*ed* to grow at room temperature," and "Air *was* removed from the chamber and the mice *died*, which *proves* that mice *require* air." In reporting statistics and calculations, it is correct to say "The values for the ABC cells *are* statistically significant, indicating that the drug inhibit*ed* . . . ."

For an in-depth discussion of tense in scientific writing, see p. 207–209 in *How To Write and Publish a Scientific Paper*, 5th ed.

### Abbreviations

**General.** Abbreviations should be used as an aid to the reader, rather than as a convenience to the author, and therefore their **use should be limited**. Abbreviations other than those recommended by the IUPAC-IUB (*Bio-*

*chemical Nomenclature and Related Documents*, 1978) should be used only when a case can be made for necessity, such as in tables and figures.

It is often possible to use pronouns or to paraphrase a long word after its first use (e.g., "the drug" or "the substrate"). Standard chemical symbols and trivial names or their symbols (folate, Ala, Leu, etc.) may also be used.

It is strongly recommended that all abbreviations except those listed below be introduced in the first paragraph in Materials and Methods. Alternatively, define each abbreviation and introduce it in parentheses the first time it is used; e.g., "cultures were grown in Eagle minimal essential medium (MEM)." Generally; eliminate abbreviations that are not used at least three times in the text (including tables and figure legends).

**Not requiring introduction.** In addition to abbreviations for Système International d'Unités (SI) units of measurement, other common units (e.g., bp, kb, and Da), and chemical symbols for the elements, the following should be used without definition in the title, abstract, text, figure legends, and tables: DNA (deoxyribonucleic acid); cDNA (complementary DNA); RNA (ribonucleic acid); cRNA (complementary RNA); RNase (ribonuclease); DNase (deoxyribonuclease); rRNA (ribosomal RNA); mRNA (messenger RNA); tRNA (transfer RNA); AMP, ADP, ATP, dAMP, ddATP, GTP, etc. (for the respective 5′ phosphates of adenosine and other nucleosides) (add 2′-, 3′-, or 5′- when needed for contrast); ATPase, dGTPase, etc. (adenosine triphosphatase, deoxyguanosine triphosphatase, etc.); NAD (nicotinamide adenine dinucleotide); $NAD^+$ (nicotinamide adenine dinucleotide, oxidized); NADH (nicotinamide adenine dinucleotide, reduced); NADP (nicotinamide adenine dinucleotide phosphate); NADPH (nicotinamide adenine dinucleotide phosphate, reduced); $NADP^+$ (nicotinamide adenine dinucleotide phosphate, oxidized); poly(A), poly(dT), etc. (polyadenylic acid, polydeoxythymidylic acid, etc.); oligo(dT), etc. (oligodeoxythymidylic acid, etc.); UV (ultraviolet); PFU (plaque-forming units); CFU (colony-forming units); MIC (minimal inhibitory concentration); Tris [tris(hydroxymethyl)aminomethane]; DEAE (diethylaminoethyl); EDTA (ethylenediaminetetraacetic acid); EGTA [ethylene glycol-bis (β-aminoethyl ether)-*N,N,N′,N′*-tetraacetic acid]; HEPES (*N*-2-hydroxyethylpiperazine-*N*′-2-ethanesulfonic acid); PCR (polymerase chain reaction); and AIDS (acquired immunodeficiency syndrome). Abbreviations for cell lines (e.g., HeLa) also need not be defined.

The following abbreviations should be used without definition in tables:

amt (amount)
approx (approximately)
avg (average)
concn (concentration)
diam (diameter)
expt (experiment)
SE (standard error)
SEM (standard error of the mean)
sp act (specific activity)
sp gr (specific gravity)
temp (temperature)
exptl (experimental)
ht (height)
mo (month)
mol wt (molecular weight)
no. (number)
prepn (preparation)
SD (standard deviation)
tr (trace)
vol (volume)
vs (versus)
wk (week)
wt (weight)
yr (year)

## Reporting Numerical Data

Standard metric units are used for reporting length, weight, and volume. For these units and for molarity, use the prefixes m, μ, n, and p for $10^{-3}$, $10^{-6}$, $10^{-9}$, and $10^{-12}$, respectively. Likewise, use the prefixes c for $10^{-2}$ and k for $10^3$. Avoid compound prefixes such as mμ or μμ. Use μg/ml or μg/g in place of the ambiguous ppm. Units of temperature are presented as follows: 37°C or 324 K.

When fractions are used to express units such as enzymatic activities, it is preferable to use whole units, such as g or min, in the denominator instead of fractional or multiple units, such as μg or 10 min. For example, "pmol/min" is preferable to "nmol/10 min," and "μmol/g" is preferable to "nmol/μg." It is also preferable that an unambiguous form such as exponential notation be used; for example, "μmol $g^{-1}$ $min^{-1}$" is preferable to "μmol/g/min." Always report numerical data in the appropriate SI units.

For a review of some common errors associated with statistical analyses and reports, plus guidelines on how to avoid them, see the article by C. Olsen (Infect. Immun. 71:6689–6692, 2003).

## Isotopically Labeled Compounds

For simple molecules, labeling is indicated in the chemical formula (e.g., $^{14}CO_2$, $^3H_2O$, and $H_2{}^{35}SO_4$). Brackets are not used when the isotopic symbol is attached to the name of a compound that in its natural state does not contain the element (e.g., $^{32}S$-ATP) or to a word that is not a specific chemical name (e.g., $^{131}I$-labeled protein, $^{14}C$-amino acids, and $^3H$-ligands).

For specific chemicals, the symbol for the isotope introduced is placed in square brackets directly preceding the part of the name that describes the labeled entity. Note that configuration symbols and modifiers precede the isotopic symbol. The following examples illustrate correct usage:

[$^{14}$C]urea
[2,3-$^3$H]serine
[γ-$^{32}$P]ATP
SV40 [$^{32}$P]DNA
L-[*methyl*-$^{14}$C]methionine
[α-$^{14}$C]lysine
UDP-[U-$^{14}$C]glucose
fructose 1,6-[1-$^{32}$P]bisphosphate

JVI follows the same conventions for isotopic labeling as the *Journal of Biological Chemistry*, and more-detailed information can be found in the instructions to authors of that journal (first issue of each year).

# Guide for Authors

## AIMS AND SCOPE

*Virology* publishes the results of original basic research on viruses of animals (vertebrate and invertebrate), plants, bacteria, and yeasts/fungi. We invite articles on all areas of research, including virus replication and gene expression, virus structure and assembly (including atomic structure), virus-cell interaction (including cellular changes as a consequence of viral infection), viral pathogenesis and immunity (at both molecular and organismal levels), viral vectors/gene therapy, and molecular aspects of prevention of viral infection. Papers describing results on emerging viruses and unconventional agents will receive special attention.

## EDITORS

The editors and their areas of responsibility are given here

## CATEGORIES AND TYPES OF ARTICLES

Papers will be published in *Virology* under one of the following subheadings:

- Virus Replication/Gene Expression
- Virus Structure and Assembly
- Virus-Cell Biology
- Viral Pathogenesis and Immunity
- Gene Therapy/Viral Vectors
- Emerging Viruses/Unconventional Agents

*Virology* publishes three forms of manuscripts: (a) regular manuscripts, including short but complete studies; (b) rapid communications; and (c) minireviews.

Regular manuscripts present the results of original basic research in all areas of virology (above) that break new ground and serve as a valuable addition to the literature in the field.

A Rapid Communication is a brief, definitive report of highly significant and timely findings in the field. Authors should indicate the submission as such, and if on preliminary inspection the editor believes the paper is of a nature to warrant this category, the paper will receive very rapid review and, if acceptable, will be published within an average of 8 weeks from receipt.

Minireviews bring cutting-edge developments and themes in the field to virologists, postdoctoral fellows, graduate students, and others interested in the field. The goal of these minireviews is to focus on a sharply defined topic in an interesting area in virology or on recent research (such as two or three papers coming in a specific area of virology). The objective is to make the information accessible to researchers who work in other areas of virology. Minireviews should be pithy, that is, should not cover the field in question comprehensively but rather address fundamental concepts, challenges, and problems in the field. In summary, virologists and others, both directly in and outside the area of the minireview, should benefit from reading these minireviews. The minireviews should provide a critical view of the field. Minireviews would also be an appropriate forum for introducing new viewpoints, indicating important issues to be addressed, and challenging concepts.

## SPEED OF PUBLICATION

***Peer Review Process:*** Each editor is responsible for having manuscripts reviewed and for making the final decision concerning the disposition. Each manuscript is reviewed by at least two reviewers. All manuscripts are reviewed as rapidly as possible, and an editorial decision is usually reached within 4 to 5 weeks of the manuscript's submission.

***Publication Schedule:*** Accepted manuscripts are usually published in print within 12-14 weeks of acceptance, and within 4-5 weeks from receipt of authors corrected proofs. Please note that early publication online may occur within days of receipt of corrected proofs.

## EDITORIAL POLICIES

There are no page charges for publication in *Virology*.

Authors should understand that space limitations make it impossible to publish manuscripts that describe work that does not break new ground conceptually, particularly if the work merely mirrors work done on a closely related virus without adding significant new knowledge, such as partial sequences of related viruses, evolutionary studies based on partial sequences, or descriptions of antigenic relationships and epitopes. Exceptions will be made, however, if these data reveal new insights into the fundamental properties of the virus.

Submission of an article implies that the work described has not been published previously (except in the form of an abstract or as part of a published lecture or academic thesis), that it is not under consideration for publication elsewhere, that its publication is approved by all authors and tacitly or explicitly by the responsible authorities where the work was carried out, and that, if accepted, it will not be published elsewhere in the same form, in English or in any other language, without the written consent of the Publisher.

Publication of a research article in *Virology* is taken to imply that the authors are prepared to distribute freely to academic researchers for their own use any materials (e.g., viruses, cells, DNA clones, antibodies) used in the published experiments. Prior to publication, nucleotide sequences and protein sequences must be deposited with GenBank (Web site: http://www.ncbi.nlm.nih.gov/Genbank/) and an accession number obtained for publication in the manuscript. X-ray crystallographic coordinates must be deposited with the Protein Data Bank (Web site: http://www.rcsb.org/pdb/).

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**NEW!**
**SUBMISSION OF MANUSCRIPTS**

Authors are requested to submit their papers electronically by using online manuscript submission available at http://ees.elsevier.com/viro. This site will guide authors stepwise through the submission process. Authors can upload their articles as Microsoft (MS) Word, WordPerfect, or LaTeX files. It is also possible to submit an article in PostScript or Adobe Acrobat PDF format, but if the article is accepted, the original source files will be needed. If you submit a word processing file, the system generates an Adobe Acrobat PDF version of the article, which is used for the reviewing process.

The above represents a very brief outline of this form of submission. It can be advantageous to print this Guide for Authors section from the site for reference in the subsequent stages of article preparation.

***Submission Checklist:*** You will be asked to submit:

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- **Response to Reviews** (Resubmissions Only): Document (Word, WordPerfect, RTF, PDF, LaTeX) detailing your response to the reviewers' and editor's comments of a previously rejected manuscript that you are resubmitting.
- **Manuscript:** Single word processing (Word, WordPerfect, RTF) or LaTeX file consisting of the title page, abstract, manuscript text, and any figure/table legends.
- **Tables:** Tables should be separate from the manuscript text and can be uploaded individually or consolidated into a single file. The file description you input when uploading your table must include the table number or range (e.g., Table 1, Tables 2-4).
- **Figures:** Figures should be uploaded individually as TIF or EPS files. Although other figure formats are allowed by the system (GIF, JPEG, Postscript, PICT, PDF, Excel, and PowerPoint), they will delay the production process should your manuscript be accepted. The file description you input below when uploading your figure must include the figure number (e.g., Fig. 2A).

Please submit, with the manuscript, the names and addresses of up to 6 potential referees.

**FORMATS AND MANUSCRIPT STYLE**

It is important that the file be saved in the native format of the word processor used. The text should be in single-column format. Keep the layout of the text as simple as possible. Most formatting codes will be removed and replaced during typesetting. In particular, do not use the word processor's options to justify text or to hyphenate words. However, do use boldface, italics, subscripts, superscripts, etc. Do not embed graphically designed equations or tables, but prepare these using the word processor's facility. When preparing tables, if you are using a table grid, use only one grid for each individual table and not a grid for each row. If no grid is used, use tabs, not spaces, to align columns. To avoid unnecessary errors you are strongly advised to use the spell checking function of your word processor. See also the section on preparation of electronic illustrations.

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**ORGANIZATION AND GENERAL STYLE OF MANUSCRIPTS**

Manuscripts should be written as concisely as possible with minimum repetition between Results and Discussion and Materials and Methods and figure legends. All figures must be of a quality such that the reviewers can judge the data.

***(a) Regular Manuscripts***

The organization shown below should be followed (in the order given):

The **title page** should contain the following elements:
*The title* should be concise and informative. Titles are often used in information-retrieval systems. Avoid abbreviations and formulas where possible.
*Author names and affiliations.* Where the family name may be ambiguous (e.g., a double name), please indicate this clearly. Present the authors' affiliation addresses (where the actual work was done) below the names. Indicate all affiliations with a lowercase superscript letter immediately after the author's name and in front of the appropriate address. Provide the full postal address of each affiliation, including the country name, and, if available, the e-mail address of each author.
*Corresponding author.* Clearly indicate who is willing to handle correspondence at all stages of refereeing and publication, also post-publication. Ensure that telephone and fax numbers (with country and area code) are provided in addition to the e-mail address and the complete postal address.
*Present/permanent address.* If an author has moved since the work described in the article was done, or was visiting at the time, a present address (or permanent address) may be indicated as a footnote to that author's name. The address at which the author actually did the work must be retained as the main, affiliation address. Superscript Arabic numerals are used for such footnotes.

**Abstract.** A concise and factual abstract is required (maximum length 150 words). The abstract should summarize the main findings of the paper. An abstract is often presented separate from the article, so it must be able to stand alone. References should therefore be avoided, but if essential, they must be cited in full, without reference to the reference list.

**Keywords.** Immediately after the abstract, provide a maximum of 10 keywords, avoiding general and plural terms and multiple concepts (avoid, for example, 'and', 'of'). Be sparing with abbreviations: only abbreviations firmly established in the field may be eligible. These keywords will be used for indexing and searching purposes.

The **Introduction** should be succinct with no subheadings. It should contain material directly relevant to the research that is described and should state clearly the aims of the investigation in the light of related work. Fair citation of the work of others is essential. Authors are asked to use nomenclature approved by the International Committee for the Taxonomy of Viruses (ICTV) (Web site: http://www.ncbi.nlm.nih.gov/) the first time a virus name appears. Commonly used vernacular names may be used after viruses are first correctly identified. Genetic loci should be italicized; protein products of the loci are not italicized.

**Results** and **Discussion** may be divided by subheadings or may be combined into one section when substantial redundancy cannot be avoided in two separate sections or if a long discussion is not warranted. A Discussion section should be constructively interpretive and not restate experimental data.

**Materials and methods** should provide sufficient information to permit the work to be repeated and should be kept concise by referring to previously published procedures. With increasing studies on pathogenicity of viruses, it is important that the provenance of viruses be stated clearly.

**Acknowledgments.** Place acknowledgments, including information on grants received, before the references, in a separate section, and not as a footnote on the title page.

**References** should include only articles that have been published or are in press. Unpublished data, submitted manuscripts, or personal communications should be cited within the text. Personal communications should be documented by a letter of permission. Abstracts of work presented at meetings many not be cited. Names of authors should be mentioned in the text with year of publication in parentheses. References should be listed alphabetically at the end of the paper. Journal names should be abbreviated according to the Chemical Abstracts Service index: http://www.cas.org/.

*Text.* All citations in the text should refer to:

1. Single author: the author's name (without initials, unless there is ambiguity) and the year of publication.
2. Two authors: both authors' names and the year of publication.
3. Three or more authors: first author's name followed by "et al." and the year of publication.

Citations may be made directly (or parenthetically). Groups of references should be listed first alphabetically, then chronologically.

Examples: "as demonstrated (Allan, 1996a, 1996b, 1999; Allan and Jones, 1995). Kramer et al. (2000) have recently shown ...."

*List.* References should be arranged first alphabetically and then further sorted chronologically if necessary. More than one reference from the same author(s) in the same year must be identified by the letters "a", "b", "c", etc., placed after the year of publication.

Reference to a journal publication:
Park, J., Nadeau, P.E., Mergia, A., 2002. A minimal genome simian foamy virus type 1 vector system with efficient gene transfer. Virology 302, 236-244.

Reference to a book:

Hagag, N., Viola, M.V., 1993. Chromosome Microdissection and Cloning: A Practical Guide. Academic Press, San Diego.

Reference to a chapter in an edited book:
Mettam, G.R., Adams, L.B., 1999. How to prepare an electronic version of your article. In: Jones, B.S., Smith, R.Z. (Eds.), Introduction to the Electronic Age. E-Publishing Inc., New York, pp. 281-304.

*Citations in the text.* Please ensure that every reference cited in the text is also present in the reference list (and vice versa). Any references cited in the abstract must be given in full. Unpublished results and personal communications should not be in the reference list, but may be mentioned in the text. Citation of a reference as "in press" implies that the item has been accepted for publication.

*Citing and listing of Web references.* As a minimum, the full URL should be given. Any further information, if known (author names, dates, reference to a source publication, etc.), should also be given.

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Duerst, R.J., Morrison, L.A., 2004. Herpes simplex virus 2 virion host shutoff protein interferes with type I interferon production and responsiveness. Virology, doi:10.1016/j.virol.2004.01.019.

**DNA sequences and GenBank accession numbers.** Authors wishing to enable other scientists to use the accession numbers cited in their papers via links to these sources should type this information in the following manner:

*For each and every* accession number cited in an article, authors should type the accession number in **bold, underlined text**. Letters in the accession number should always be capitalized (see example below). This combination of letters and format will enable the typesetter to recognize the relevant texts as accession numbers and add the required link to GenBank's sequences.

**Example:** GenBank accession nos. **AI631510, AI631511**, **AI632198**, and **BF223228**), a B-cell tumor from a chronic lymphatic leukemia (GenBank accession no. **BE675048**), and a T-cell lymphoma (GenBank accession no. **AA361117**).

Authors are encouraged to check accession numbers used very carefully. **An error in a letter or number can result in a dead link.**

In the final version of the ***printed* article,** the accession number text will not appear bold or underlined. In the final version of the ***electronic* copy,** the accession number text will be linked to the appropriate source in the NCBI databases, enabling readers to go directly to that source from the article.

**Tables** should be separate from the manuscript text and numbered consecutively in accordance with their appearance in the text. Tables can be uploaded individually or consolidated into a single file. The file description you input below when uploading your table must include the table number or range (e.g., Table 1, Tables 2-4). Place footnotes to tables below the table body and indicate them with superscript lowercase letters. Avoid vertical rules. Be sparing in the use of tables and ensure that the data presented in tables do not duplicate results described elsewhere in the article.

**Figure legends** should contain a brief description of the experiment performed so that the figure can be understood without reference to the body of the text. However, the legend should not repeat Materials and Methods or contain interpretive statements.

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TIFF: Color or gray-scale photographs (halftones): always use a minimum of 300 dpi.
TIFF: Bitmapped line drawings: use a minimum of 1000 dpi.
TIFF: Combinations bitmapped line/halftone (color or gray scale): a minimum of 500 dpi is required.
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- Supply files that are too low in resolution.
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***(b) Rapid Communications***

Manuscripts in general should be no longer than 12 double-spaced typewritten pages, containing an abstract of approximately 100 words, a one-paragraph introduction, Results, a concise Discussion section, and an abbreviated Materials and Methods section. A maximum of 20 references and four items for the display of data (any combination of figures and tables) will be allowed.

Rapid Communications will be reviewed within 1 to 2 weeks. No significant revisions will be permitted. PDF proofs will be e-mailed to authors. Corrections must be returned with 48 hours. Rapid communications will appear in a special section at the front of the journal. Rapid communications are distinct from the previously published "short communications." This category is not intended for reporting preliminary studies or brief studies of a descriptive nature.

***(c) Minireviews***

The minireviews will be short (2-4 pages). Inclusion of figures/cartoons to illustrate points is strongly encouraged. The minireview should also direct the reader to a few key papers in the field, which come under the heading "Selected Reading." There is no formal Reference section.

***Cover illustrations***

Authors are encouraged to submit interesting figures for possible publication on the front cover of an issue of this journal; the figure should be related to the author's article.

**MANUSCRIPT CHECKLIST**

It is hoped that this list will be useful during the final checking of an article prior to submitting it to the journal for review.

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- Full postal address
- Telephone and fax numbers
- All necessary files have been uploaded
- Keywords
- All figure captions
- All tables (including title, description, footnotes) are provided

*Further considerations*

- Manuscript has been "spell-checked."
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- All references mentioned in the Reference list are cited in the text, and vice versa.
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# Appendix B

# UNITED STATES PATENT AND TRADEMARK OFFICE

## BEFORE THE BOARD OF PATENT APPEALS AND INTERFERENCES

Ex parte NORIMITSU SAITO and MING ZHAO

Appeal No. 2005-1442
Application No. 09/734,786

ON BRIEF

Before ELLIS, SCHEINER, and GRIMES, Administrative Patent Judges.

GRIMES, Administrative Patent Judge.

## DECISION ON APPEAL

This appeal involves claims to a method of introducing a nucleic acid into a subject by modifying and transplanting hair follicles. The examiner has rejected the claims as nonenabled. We have jurisdiction under 35 U.S.C. § 134. Because the examiner has not shown that undue experimentation would have been required to practice the claimed method, we reverse.

## Background

The specification discloses that "histocultured tissues, including tissues containing hair follicles, can be successfully modified genetically ex vivo and then transplanted successfully into an intact mammalian subject. The success of the

modification is enhanced by treating the histocultured tissues with collagenase prior to genetic modification." Pages 2-3.

The specification states that

> [a]lthough it is advantageous to treat the cultured tissue with collagenase in order to enhance the ability of the tissue to accept heterologous nucleic acids, the treatment is not so severe as to destroy completely the integrity of the three-dimensional array.
>
> The three-dimensional histoculture can be assembled from any tissue, including skin, especially skin containing hair follicles, lymphoid tissue, or tumor tissue. The choice of tissue will depend on the nature of the treatment contemplated. . . .
>
> For example, hair follicles are useful recipients of genes intended to affect the growth or quality of hair, but also are able to produce immunogens and other products that may be useful to the organism taken as a whole.

Page 4.

The specification provides a working example in which DNA encoding green fluorescent protein (GFP) was introduced into hair follicles of histocultured mouse skin; the percentage of GFP-expressing hair follicles ranged from 22% to 67%. See pages 11-12. In a second working example, hair follicles in skin samples were transfected with GFP-encoding DNA and grafted onto recipient mice. The results showed that "the percentage of hair follicles with GFP fluorescence in collagenase-treated skin was 5.7 times greater than in hair follicles of untreated skin." Pages 14-15. Fluorescence was detected for at least 10 days after grafting. Figure 3B.

## Discussion

### 1. Claim construction

Claims 1 and 11 are representative of the claims on appeal and read as follows:

1. A method to introduce a nucleic acid molecule into a mammalian subject which method comprises

transplanting into the dermis of said subject at least one hair follicle that has been modified ex vivo to contain said nucleic acid molecule.

11. A method to introduce a nucleic acid molecule into a mammalian subject which method comprises transplanting into the corresponding tissue of said mammal a histocultured intact tissue that has been modified ex vivo to contain said nucleic acid molecule;

wherein said histoculture has been treated with collagenase prior to modifying said tissue with the nucleic acid.

Thus, claim 1 is directed to a method of introducing a nucleic acid into a mammal by modifying a hair follicle ex vivo to contain the nucleic acid and transplanting the hair follicle to the mammal. Claim 1 does not explicitly require that the nucleic acid be expressed or provide any particular benefit to the mammal.

Claim 11 is similar to claim 1 but encompasses treating tissues other than hair follicles; in addition, claim 11 requires that the tissue be treated with collagenase before being modified with the nucleic acid.

### 2. Enablement

The examiner rejected claims 1-8, 11, 13-15, 17, and 19, all of the claims remaining, under 35 U.S.C. § 112, first paragraph, on the basis that the specification does not enable those skilled in the art to practice the claimed method without undue experimentation. The examiner considered the factors set out in In re Wands, 858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988), and concluded that

> [d]ue to the art recognized unpredictability of achieving therapeutic levels of gene expression following direct or indirect administration of nucleic acids and the lack of guidance provided by the specification for the parameters affecting delivery and expression of therapeutic amounts of DNA into the cells using ex vivo gene transfer into histocultured organs or tissues, it would require undue experimentation to practice the instant invention.

Examiner's Answer, page 10

Appellants argue that the claims are directed to a method of genetically modifying tissues ex vivo and transplanting the modified tissue into a subject, and therefore do not require achieving therapeutic levels of gene expression. Appeal Brief, page 5. Appellants point to the specification's discussion of prior art techniques and working examples as guidance to those skilled in the art. Appellants assert that "[t]he pending claims are fully supported by the ample amount of knowledge available in the relevant art when the present application was filed and the guidance provided in the specification." Id., page 7.

We agree with Appellants that the examiner has not adequately shown that undue experimentation would have been required to practice the claimed method. The examiner bears the initial burden of showing that a claimed invention is nonenabled. See In re Wright, 999 F.2d 1557, 1561-62, 27 USPQ2d 1510, 1513 (Fed. Cir. 1993) ("[T]he PTO bears an initial burden of setting forth a reasonable explanation as to why it believes that the scope of protection provided by that claim is not adequately enabled by the description of the invention provided in the specification of the application.").

"[T]o be enabling, the specification of a patent must teach those skilled in the art how to make and use the full scope of the claimed invention without 'undue experimentation.'" In re Wright, 999 F.2d 1557, 1561, 27 USPQ2d 1510, 1513 (Fed.

Cir. 1993). "That some experimentation may be required is not fatal; the issue is whether the amount of experimentation required is 'undue.'" In re Vaeck, 947 F.2d 488, 495, 20 USPQ2d 1438, 1444 (Fed. Cir. 1991).

The enablement analysis must be focused on the product or method defined by the claims. "Title 35 does not require that a patent disclosure enable one of ordinary skill in the art to make and use a perfected, commercially viable embodiment absent a claim limitation to that effect." CFMT, Inc. v. Yieldup Int'l Corp., 349 F.3d 1333, 1338, 68 USPQ2d 1940, 1944 (Fed. Cir. 2003).

Here, the examiner has acknowledged that the claims are not limited to therapeutic methods, but argues that because therapeutic methods are encompassed by the claims, such methods must be enabled in order for the full scope of the claims to be enabled. See the Examiner's Answer, page 12.

The examiner's reasoning is logical but not entirely consistent with the case law: enabling the "full scope" of a claim does not necessarily require enabling every embodiment within the claim. See, e.g., Atlas Powder Co. v. E.I. Du Pont De Nemours & Co., 750 F.2d 1569, 1576, 224 USPQ 409, 414 (Fed. Cir. 1984): "Even if some of the claimed combinations were inoperative, the claims are not necessarily invalid. . . . Of course, if the number of inoperative combinations becomes significant, and in effect forces one of ordinary skill in the art to experiment unduly in order to practice the claimed invention, the claims might indeed be invalid." Atlas Powder concerned claims to a product, not a method as here, but the same principle applies – a claimed method does not lack enablement merely because it cannot be practiced under some circumstances or to achieve some particular result.

In re Cortright, 165 F.3d 1353, 49 USPQ2d 1464 (Fed. Cir. 1999), is instructive. In Cortright, the applicant claimed a method of "treating scalp baldness with an antimicrobial to restore hair growth." Id. at 1355, 49 USPQ2d at 1465. The Board reversed a rejection for lack of utility, but entered a new rejection for lack of enablement, on the basis that "restor[ing] hair growth" required returning the user's hair to its original state (a full head of hair). See id. "Because Cortright's written description discloses results of only 'three times as much hair growth as two months earlier,' 'filling-in some,' and 'fuzz,' the board reasoned, it does not support the breadth of the claims." Id. at 1358, 49 USPQ2d at 1467.

The court disagreed with the Board's claim interpretation, holding that "one of ordinary skill would construe this phrase [restoring hair growth] as meaning that the claimed method increases the amount of hair grown on the scalp but does not necessarily produce a full head of hair." Id. at 1359, 49 USPQ2d at 1468. The court concluded that the claims, so construed, were enabled. Id.

As with the present claims, the claims in Cortright encompassed a method of obtaining results that might be difficult to achieve: here, therapeutically effective gene therapy; in Cortright, complete restoration of hair growth. However, as in Cortright, the present claims do not require that particular result: the present claims require only introducing or delivering a nucleic acid; Cortright's claims required only some restoration of hair growth.

The court in Cortright did not dispute the Board's conclusion that completely restoring hair growth using Bag Balm® would require undue experimentation. See id. at 1357, 49 USPQ2d at 1467. The court nonetheless concluded that the claimed method

was not nonenabled merely because it encompassed one difficult-to-achieve outcome. The same reasoning applies here: the examiner may be correct that achieving clinically useful gene therapy using the claimed method would require undue experimentation, but the claims are not nonenabled merely for encompassing that difficult-to-achieve outcome.

The claims are directed to methods of introducing a nucleic acid into a mammalian subject or delivering a nucleic acid to a hair follicle or intact tissue. The examiner has not adequately explained why the specification does not enable those skilled in the art to introduce a nucleic acid into a mammalian subject, or deliver a nucleic acid to a hair follicle or intact tissue, without undue experimentation. We therefore reverse the rejection for nonenablement.

REVERSED

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|---|---|
| Joan Ellis<br>Administrative Patent Judge | ) |
| Toni R. Scheiner<br>Administrative Patent Judge | ) BOARD OF PATENT<br>) APPEALS AND<br>) INTERFERENCES |
| Eric Grimes<br>Administrative Patent Judge | ) |

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# Appendix C

# UNITED STATES PATENT AND TRADEMARK OFFICE

## BEFORE THE BOARD OF PATENT APPEALS AND INTERFERENCES

Ex parte RAYMOND H. BOUTIN

Appeal No. 2006-1879
Application No. 10/010,114

ON BRIEF

Before SCHEINER, GRIMES, and LEBOVITZ, Administrative Patent Judges.

GRIMES, Administrative Patent Judge.

DECISION ON APPEAL

This appeal involves claims to a method of transferring nucleic acids into cells, which the examiner has rejected as nonenabled. We have jurisdiction under 35 U.S.C. § 134. Because we conclude that enabling the claimed method does not require providing therapeutically effective gene therapy, we reverse.

Background

Methods for delivering nucleic acids to cells in vivo face several problems: "persistence in the biophase of the organism for a sufficient time to reach the target cell; recognition of the target cell and means for mediating transport of the genetic material through the cell membrane and into the cytoplasm of the cell; avoidance of degradation

within the cell by the reticuloendothelial system; and transport to and through the nuclear membrane into the nucleus of the cell where transcription of the genetic material can take place." Specification, page 2, lines 5-14. The specification discloses a "multifunctional molecular complex for the transfer of a nucleic acid composition to a target cell comprising . . . : 1) said nucleic acid composition; 2) one or more cationic polyamine components . . . ; [and] 3) one or more endosome membrane disruption promoting components." Page 12, lines 2-9.

"The core, or backbone[,] of the transfer moiety is the cationic polyamine, containing between 3 and 12 amines." Page 23, lines 17-18. The function of the cationic polyamine is "to overcome the incompatibility arising from the hydrophilic nature of the nucleic acid molecule and the lipophilic nature of the cell membrane." Id., lines 20-23.

"The next component of the transfer moiety is the endosome membrane disruption promoting component. . . . This can either comprise one or more lipophilic long chain alkyl groups attached through one or more of the nitrogen atoms of said polyamine, or can comprise a bridging group . . . through which there is attached a fusogenic peptide, or cholic acid or cholesteryl or derivative compound." Page 25, lines 28-37. This component "prevent[s] degradation of the nucleic acid molecule in a lysosome," page 16, lines 27-28, by "permit[ting] the complex to escape from the endosome, whereupon it can migrate into the nucleus of the target cell, and release the nucleic acid composition, whose genetic information can then be transcribed within said nucleus." Page 34, lines 2-6.

## Discussion

### 1. Claims

Claims 1, 2, 5-9, and 17-52 are on appeal. Claims 3 and 4 are also pending; claim 4 has been objected to but not rejected, and claim 3 has been withdrawn from consideration by the examiner.

Claim 1 is representative and reads as follows:

> 1. A method for the transfer of a nucleic acid composition to cells, comprising the step of introducing a multifunctional molecular complex into cells,
>
> wherein said multifunctional molecular complex comprises:
>
> A) a nucleic acid composition; and
> B) a transfer moiety comprising
>
> (i) one or more cationic polyamine components, wherein each cationic polyamine is non-covalently bound to said nucleic acid composition and comprises from three to twelve nitrogen atoms; and
>
> (ii) one or more endosome membrane disruption promoting components independently selected from (a) at least one lipophilic long chain alkyl group or (b) a fusogenic peptide, cholic acid or cholesterol group or a derivative thereof;
>
> wherein said multifunctional molecular complex transfers said nucleic acid composition to said cells.

Thus, claim 1 is directed to a "method for the transfer of a nucleic acid composition to cells." The claim is not limited to cells in culture or in a subject, so the claim encompasses both in vitro and in vivo methods. The claim comprises "introducing . . . into cells" a multifunctional complex comprising a nucleic acid composition; a cationic polyamine comprising three to twelve nitrogen atoms, noncovalently bound to the nucleic acid composition; and an endosome disrupting agent (which can be a

lipophilic long chain alkyl group, a fusogenic peptide, cholic acid, a cholesteryl group, or a derivative) attached to a nitrogen of the polyamine component via specified linkages.

2. Enablement

The examiner rejected claims 1, 2, 5-9, and 17-52 under 35 U.S.C. § 112, first paragraph, for nonenablement. The examiner focused on the aspect of the claimed method that involves transferring a nucleic acid encoding a therapeutic protein into cells.[1] The examiner concluded that the specification is enabling for a method of transferring a nucleic acid encoding a therapeutic protein into cells in vitro but is not enabling for the same method carried out in vivo. See the Examiner's Answer, page 3.

The examiner reasoned that "[t]he in vivo aspect of claims 1, 2, 5-9 and 17-52 is interpreted as gene therapy as the specification does not disclose a use for delivering a therapeutic protein other than for therapeutic purposes." Id. The examiner noted that the instant application has an effective filing date of September 28, 1994,[2] and cited several references as evidence that undue experimentation would have been required to successfully carry out gene therapy as of that date. Id., pages 4-6.

The examiner noted that the specification does not "disclose any particular DNA sequences that can be administered by applicant's claimed methods" to treat any specific disease. Id., page 6. The examiner summarized the most relevant working examples:

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[1] The examiner restricted the claims based on the type of protein encoded by the transferred nucleic acid. See the restriction requirement mailed August 13, 2003. Appellant elected the claims directed to a method of transferring a nucleic acid encoding a therapeutic agent. See the paper filed September 11, 2003. The examiner has stated that "[b]ased on this election . . . claims 1, 2[,] 4-9, [and] 17-52, are interpreted as methods of delivering a therapeutic agent using applicant's novel multifunctional molecular complex." Examiner's Answer, pages 7-8.

[2] The instant application claims benefit under 35 U.S.C. § 120 of the filing date of application serial number 08/314,060, filed September 28, 1994.

> Example 11 teaches the expression of lacZ when a plasmid comprising a β-galactosidase gene complexed to a transfer moiety of the invention is injected into mouse thigh muscle. . . . Example 12 teaches the finding of hepatitis B [virus] surface antigen in the blood [of] mice injected i.v. with a multifunctional molecular complex comprising a plasmid containing a hepatitis B virus surface antigen gene complexed to a transfer moiety of the invention.

Id., pages 6-7. The examiner found that these examples did not provide sufficient guidance, however, because "in neither case does the expression of the delivered gene result in an alleviation of a symptom of any disease." Id., page 7.

Appellant argues that "[s]ince the claims do not require a therapeutic effect, Applicant need not demonstrate such an effect in order to enable the claimed subject matter." Appeal Brief, page 4. Appellant argues that he "need[ ] only establish that the application enable[s] one of ordinary skill in the art to make and use a method for transfer[ring] nucleic acid compositions to cells . . . without undue experimentation." Id. Appellant argues that the references cited by the examiner are not applicable because they describe different methods of delivering nucleic acids to cells. Id., page 5. Finally, Appellant relies on a declaration submitted under 37 CFR § 1.132, which is said to provide additional examples of in vivo transfer of nucleic acids using the claimed method. See id., pages 7-9

The examiner bears the initial burden of showing that a claimed method is not enabled. See In re Wright, 999 F.2d 1557, 1561-62, 27 USPQ2d 1510, 1513 (Fed. Cir. 1993) ("[T]he PTO bears an initial burden of setting forth a reasonable explanation as to why it believes that the scope of protection provided by that claim is not adequately enabled by the description of the invention provided in the specification of the application.").

The invention that must be enabled to satisfy § 112 is the invention defined by the claims. See CFMT, Inc. v. Yieldup Int'l Corp., 349 F.3d 1333, 1338, 68 USPQ2d 1940, 1944 (Fed. Cir. 2003) ("Title 35 does not require that a patent disclosure enable one of ordinary skill in the art to make and use a perfected, commercially viable embodiment absent a claim limitation to that effect."). Thus, when the claims are not directed to a method that achieves a therapeutically useful result, achieving such a result is not required for the claims to be enabled.

Here, the claims, as restricted, are directed to a "method for the transfer of a nucleic acid composition [encoding a therapeutic agent] to cells." Thus, while the claims read on gene therapy methods, they do not require producing a clinically effective therapeutic response. Cf. In re Cortright, 165 F.3d 1353, 49 USPQ2d 1464 (Fed. Cir. 1999) (claims to a method of "treating scalp baldness" could be enabled even if the method did not produce a full head of hair).

The examiner argues, however, that the specification must teach those skilled in the art how to use the claimed method to produce a therapeutically useful result because

> the only use disclosed for in vivo delivery is [ ] for therapeutic purposes. . . . Thus, while the specification enables delivery and expression in cells in culture or cells in vitro, the method of delivering has no enabled use for delivery to cells in an animal, patient or subject[;] that is[,] in vivo. There is no evidence that the method results in sufficient delivery of a nucleic acid in vivo to offer a therapeutic effect. The specification offers no use for mere delivery of a therapeutic agent in vivo absent a therapeutic effect.

Examiner's Answer, page 8. As we understand it, the examiner does not dispute that the specification enables those skilled in the art to transfer nucleic acids into cells in

vivo, but she argues that transferring a nucleic acid encoding a therapeutic protein does not produce a useful result unless it confers a therapeutic benefit.

The examiner's reasoning highlights the incorporation into § 112 of the utility requirement of 35 U.S.C. § 101: to be enabled, a claimed method must be disclosed sufficiently to allow those skilled in the art to carry out the recited steps and, in addition, the result of the claimed method must have a specific and substantial utility. See In re Fisher, 421 F.3d 1365, 1378, 76 USPQ2d 1225, 1235 (Fed. Cir. 2005) ("It is well established that the enablement requirement of § 112 incorporates the utility requirement of § 101."); In re Kirk, 376 F.2d 936, 942, 153 USPQ 48, 53 (CCPA 1967) ("[S]urely Congress intended § 112 to pre-suppose full satisfaction of the requirements of § 101. Necessarily, compliance with § 112 requires a description of how to use presently useful inventions, otherwise an applicant would anomalously be required to teach how to use a useless invention.").

The examiner's reasoning is logical but we do not agree that it applies to the instant claims. The specification describes experiments in which exogenous DNA was transferred, using the claimed method, to muscle cells and liver cells in vivo. See pages 77-78. The examiner has not disputed the accuracy of these working examples, but points out that the transferred DNAs did not encode therapeutic proteins and the specification does not describe therapeutically effective gene therapy.

The examiner has cited several references to show that clinical application of gene therapy faced many hurdles in 1994. The examiner has characterized the references as showing that delivering therapeutic genes to cells in vivo and ensuring

adequate expression of the gene products were major areas of unpredictability at the time of filing. See the Examiner's Answer, pages 4-6.

We can accept, for discussion purposes, (1) that the references show that using gene therapy to produce a therapeutically effective result would have required undue experimentation in 1994, and (2) that gene therapy is the only in vivo use disclosed in the specification for the claimed method. Even given those two premises, however, we do not agree that the evidence shows that the claimed method was not enabled as of its effective filing date.

As discussed above, the claims are not directed to a method of carrying out gene therapy, but to a method of transferring nucleic acids into cells. That is, the claimed method is directed to one step in, for example, a gene therapy method. The claimed method is disclosed to overcome some of the problems discussed in the references cited by the examiner. See the specification, pages 2 and 16:

> The problems faced by [nonviral vectors or carriers] include . . . means for mediating transport of the genetic material through the cell membrane and into the cytoplasm of the cell; avoidance of degradation within the cell by the reticuloendothelial system; and transport to and through the nuclear membrane into the nucleus of the cell where transcription of the genetic material can take place.
> . . .
> This multifunctional molecular complex comprises essentially the combination of two key elements, (I) the nucleic acid composition which it is desired to transfer to the target cell, and (II) the transfer moiety, which . . . comprises several components whose function is . . . ii) to overcome the incompatibility arising from the hydrophilic nature of the nucleic acid molecule and the lipophilic nature of the cell membrane so that the former can pass through the latter; and iii) to prevent degradation of the nucleic acid molecule in a lysosome of said target cell, by disrupting the pre-lysosome, endosome formation stage.

The examiner has stated that the in vitro embodiments encompassed by the claims are enabled, and has not disputed the accuracy of the specification's in vivo working examples. There seems to be no dispute, therefore, that the claimed method results in the transfer and expression of nucleic acids in targeted cells. We cannot agree that such a result must provide a therapeutic effect in order to be useful.

A method that overcomes some of the problems plaguing the field of gene therapy would seem to be a useful advance, even if the advance is incremental and does not resolve all of the problems facing the field. Such a method is useful to those skilled in the art even if it is not sufficient, by itself, to allow immediate practice of gene therapy. A method that enhances the efficiency of transfer of nucleic acids to cells in vivo, as the present method is said to do, provides a valid research tool that those skilled in the art could use in carrying out experiments involving transferring nucleic acids to cells in vivo.

The present claims are different from, for example, the invention at issue in In re Fisher, 421 F.3d 1365, 76 USPQ2d 1225 (Fed. Cir. 2005). The applicant in that case claimed expressed sequence tags (ESTs) from genes of unknown function. See id. at 1370, 76 USPQ2d 1231. The court concluded that "the claimed ESTs act as no more than research intermediates that may help scientists to isolate the particular underlying protein-encoding genes and conduct further experimentation on those genes. . . . Accordingly, the claimed ESTs are . . . mere 'object[s] of use-testing,' to wit, objects upon which scientific research could be performed with no assurance that anything useful will be discovered in the end." Id. at 1373, 76 USPQ2d 1231.

The Fisher court considered the applicant's argument that an EST is a research tool, like a microscope, but found the analogy inapt: "[A] microscope has the specific benefit of optically magnifying an object to immediately reveal its structure. One of the claimed ESTs, by contrast, can only be used to detect the presence of genetic material having the same structure as the EST itself. It is unable to provide any information about the overall structure let alone the function of the underlying gene." Id. at 1373, 76 USPQ2d 1231. The court concluded that "Fisher's asserted uses are insufficient to meet the standard for a 'substantial' utility under § 101." Id. at 1373, 76 USPQ2d 1231.

The ESTs at issue in Fisher lacked substantial utility because they were useful only for conducting experiments on the genes of which the ESTs were part; they were not useful for conducting research generally but only for conducting research to learn more about the ESTs themselves and the genes from which they were derived. Here, by contrast, the claimed method is broadly useful for transferring nucleic acids into cells. The instant claims are directed to a completed invention, not a "research intermediate" as in Fisher, that can be used to carry out research using a variety of nucleic acids, cells, and subjects. Thus, the instantly claimed method is a valid research tool that can be used to carry out research in general rather than research limited to discovering information about the claimed invention itself.

Summary

We do not agree with the examiner that enabling the instant claims requires enabling therapeutically effective gene therapy. The specification provides adequate guidance to enable those skilled in the art to use the claimed method to transfer nucleic

acids to cells, and that is all that the claims require. The rejection for lack of enablement is reversed.

REVERSED

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|---|---|
| Toni R. Scheiner<br>Administrative Patent Judge | ) |
| Eric Grimes<br>Administrative Patent Judge | ) BOARD OF PATENT<br>) APPEALS AND<br>) INTERFERENCES |
| Richard M. Lebovitz<br>Administrative Patent Judge | ) |

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